Calcium supplementation in Article BIOCELL colorectal cancer prevention: A systematic meta-analysis of adverse events	
Authors	**XUE MEI LUO, SHAHANAVAJ KHAN, ABDUL MALIK, FAHAD M. ALDAKHEEL, ANIS AHMAD CHAUDHARY, SHOUKI BAZARBASHI, FATEMEH TABATABAIE**
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Abstract: Despite the multiple systematic reviews and meta-analyses accumulating evidence on the preventive effect of calcium supplementation for colorectal cancer, most of the associated adverse effects are not systematically analyzed. The aim of the study is evaluating adverse events associated with calcium supplementation for colorectal cancer prevention through a systematic meta-analysis. We searched Medline, PubMed Central, EMBASE (Excerpta Medica database), Scopus, Cochrane Central Register of Controlled Trials, and Web of Science published in English from database inception up to 31 July 2019. In the current systematic meta-analysis, we included human studies (including cohort studies, clinical trials, case-control studies) on supplementation of calcium in patients with or at risk of colorectal cancer. Assessment of the quality of included studies was performed by Jadad score. Information on the patient population, number of enrolled subjects in each group, dose of calcium supplementation, duration of calcium supplementation, and reported adverse events were gathered. The data were pooled for incidence rates for any adverse event during the study period regardless of causality association. We identified 6 studies, comprising 4583 participants that met the inclusion criteria. Meta-analysis on pooled incidence rates for adverse event during study period showed no statistically significant increased risk for cancer (OR = 0.92, 95% CI: 0.70–1.21, *P* = 0.577; I2 = 0.0%, *P* = 0.731), coronary revascularization (OR = 1.12, 95% CI: 0.79–1.59, *P* = 0.492; I2 = 0.0%, *P* = 0.957), myocardial infarction (OR = 0.81, 95% CI: 0.34–1.91, *P* = 0.634; I2 = 67.9%, *P* = 0.047), stroke (OR = 0.75, 95% CI: 0.42–1.33, *P* = 0.332, I2 = 0.00%, *P* = 0.717), Transient Ischemic Attack (TIA) (OR = 1.37, 95% CI: 0.28–6.51, *P* = 0.692, I2 = 81.9%, *P* = 0.002), urolithiasis (OR = 1.23, 95% CI: 0.75–2.01, *P* = 0.410; I2 = 0.0%, *P* = 0.851), fracture (OR = 0.98, 95% CI: 0.70–1.37, *P* = 0.938; I2 = 37.8%, *P* = 0.152) and death (OR = 1.05, 95% CI: 0.71–1.56, *P* = 0.786, I2 = 12.2%, *P* = 0.317) in patients receiving calcium supplementation for colorectal cancer prevention compared to control. Based on the results of Egger test, publication bias was not observed among the studies (*P* = 0.262). The current result of the meta-analysis on human studies reporting adverse events associated with calcium supplementation for the prevention of colorectal

cancer demonstrated no statistically significant increased risk for the development of adverse events compared to control groups.